EXHIBIT A

Duke | OFFICE of AUDIT, RISK & COMPLIANCE

Duke University
Research Compliance Assurance Review Executive Summary
Jiang Pro000009555 and Pro000014033
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Clinical Research Unit Management

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ENGAGEMENT TEAM

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INVESTIGATION SUMMARY

OBJECTIVE AND BACKGROUND

At the request of [redacted], M.D. and Wei Jiang, M.D., the Duke Office of Audit, Risk and Compliance (OARC) Research Compliance Assurance (RCA) section assessed compliance with Good Clinical Practice (GCP), applicable U.S. Food and Drug Administration (FDA) regulatory requirements, and institutional policies for protocols Pro000009555, Responses of Myocardial Ischemia to Escitalopram Treatment, and Pro000014033, Research Database/Repository for Blood Samples in Understanding Pathophysiological Mechanisms of Mental Stress-Induced Myocardial Ischemia (MSIMI). RCA conducted this review after the Department of Psychiatry and Behavioral Sciences (Psychiatry) assistant research practice manager noted eligibility, data quality and regulatory issues during an internal quality assurance (QA) review of Pro000009555.

RCA visited the Psychiatry research offices in the Duke Clinics building June 4 through June 13, 2018 and July 3 through July 7, 2018. RCA also visited the Investigational Drug Services (IDS) in the Department of Pharmacy on June 12, 2018. RCA reviewed regulatory documents specific to both studies and drug accountability logs for Pro000009555. Subject study records for 17 of the 310 subjects were selected for initial review. An additional eight subjects were selected after eligibility and data quality issues were identified in the first sample, for a total of 8.1%. Subject records reviewed covered the entire four-year enrollment period and work performed by the majority of research staff listed on the delegation of authority (DOA) log.

RISK AND AREA IMPACT

Pro000009555 is a single center, double-blind randomized study with a placebo arm to assess the efficacy of escitalopram on MSIMI in patients with stable ischemic heart disease (IHD). The study also examines the effects of escitalopram on depression symptoms, platelet activity and cardiovascular stress response in relationship to MSIMI. Pro000009555 is a principal investigator (PI)-initiated study funded by National Heart, Lung and Blood Institute (NHLBI) grant RHL085704 and is referred to as the REMIT trial.

Pro000014033 created a repository for specimens collected during the primary trial intended for use in future research studies; it is a PI-initiated and institutionally funded trial, referred to as the REMIT Repository trial.

OARC notes that these are two related but separate Duke University Health System (DUHS) Institutional Review Board (IRB)-approved trials.

The REMIT trial involves a widely used antidepressant in subjects with MSIMI, thereby lowering the overall patient safety risk profile. Since the data is published and both protocols are still active, there may be risk associated with reproducibility of results and integrity of current and/or future publications stemming from data quality issues.

EXECUTIVE SUMMARY RESULTS

Report results are based on information provided to the RCA team at the time of review, as well as subsequent requests for information needed to conclude on protocol compliance status. RCA recommendations reflect actions needed to achieve compliance with the protocols and GCP, as well as preventative measures to minimize issues going forward. RCA discussed these recommendations with representatives from the Duke Office of Clinical Research (DOCR) and the IRB. Subsequent implementation is left to the discretion of the IRB and Psychiatry leadership.

Overall, we observed no significant patient safety concerns. However, conflicting information and gaps in documentation indicate issues related to protocol adherence. Specific issues noted involve subject eligibility; the consenting process; data integrity; distributing, destroying and tracking drug; protocol lapse; and serious noncompliance never reported to the IRB. Of reviewed cases, OARC identified eligibility issues in 84%, procedures not performed per protocol in 92%, and documentation inconsistencies in 100%. While REMIT is a relatively low patient safety risk trial evaluating an approved and widely used antidepressant, observations

implicating data quality in this trial make it difficult to ensure research data integrity; summary observations are captured in the appendix.

The PI and study team should submit a copy of the full OARC report with all appendices and their response addressing all observations and recommendations outlined in the appendices to the IRB via iRIS. The RCA review did not include evaluation of ways data quality issues identified in this report are represented in previous publications or may affect future publications. During its evaluation, it is recommended that the IRB consult with a statistician to evaluate if and how data quality issues impact existing and future publications. The IRB and Psychiatry senior leadership will manage any further corrective action to effectively conduct compliant clinical research and collect high-quality data. DOCR should be copied on the PI response as that office may be involved in implementing the proactive recommendations. In addition, RCA recommends that DOCR support any new trial(s) administered through the PI's pending National Institutes of Health (NIH) award.

The full version of the OARC report will be sent to the PI, the department chair, the associate dean for clinical research, the director of DOCR's Operations and Study Conduct unit, and the IRB director of research review. The full report with appendices is available to others on request.

APPENDIX

REMIT Summary Results and Recommendations

Of the 310 subjects who completed the study, OARC reviewed all regulatory records, all pharmacy records, 134 consents and 25 subject files (8.1%).

Observation	Summary Results	Corrective Recommendations	Proactive Recommendations
Eligibility	• 16% of subjects reviewed were ineligible per protocol inclusion/exclusion criteria. • 44% of subjects reviewed were missing documentation required to confirm eligibility. • 24% of subjects reviewed, all toward the end of the study, were screened using additional "safety criteria" that were stricter than protocol-approved criteria. These criteria were never used to screen subjects enrolled through the first three years nor were they ever formally incorporated into the protocol. It is unclear if subjects enrolled in the first portion of the trial were at greater risk because they were not screened or enrolled using this "safety criteria."	• Provide to the IRB any missing information required to confirm eligibility for the specific subjects in question and file all additional documentation in the individual subject files. • Provide to the IRB an explanation for "safety criteria" development and use. Detail the range of patients screened using this criteria. Clarify if subjects enrolled prior to implementing the "safety criteria" were at greater risk.	• Create an eligibility checklist in the Online Collaborative Research Environment (OnCore) and use across all enrolling Psychiatry investigator-initiated trials (IITs). Ensure eligibility checklists are signed by an appropriate person listed in eIRB personnel and on the DOA log. Include fields to indicate qualifying lab values, dates of relevant screening tests, etc. • Consider requiring two faculty or staff members to sign the eligibility checklist for all or a percentage of subjects as a quality control measure.
Data Quality	• Data quality issues were observed in 100% of subject files reviewed. • Poor documentation practices were observed throughout the trial making it difficult to assess the accuracy of data transposed from the original source. ○ For many subjects, data was generated during treatment, but recorded on forms version-dated after subjects completed treatment. It is unclear if data was transcribed from earlier form versions not found in subject files or where	• Provide to the IRB a list of subjects for whom stenosis percentages were changed with accompanying source documentation and reasons supporting the changes. File copies of the source documentation supporting the changes in the subject files. • Provide an explanation for discrepancies between data in the Access database and data on forms. Clarify if changes were made directly in the database. • Reconcile all REMIT subject files. All research materials (data and sources) pertaining to the same subject should be	• All electronic case report forms (eCRFs) for IITs must have a mechanism for recording who completed the forms and a field or time stamp to record when the forms were completed. Forms should also have a mechanism to indicate if and when a particular test was not performed. These mechanisms exist within the Research Electronic Data Capture (REDCap) and its use should be considered. • REMIT required a large number of both contact hours and data collection

	original data was housed in the interim months or years. ○ Paper data did not consistently match the electronic Access database. The PI and statistician confirmed the database was used for publication. It is unclear if changes were made directly in the database or how corrections on paper forms were read by the Access scanner. ○ Multiple sets of forms were used throughout the trial with no audit trail to explain when newer versions should be used. ○ Forms were not designed to capture dates data was recorded or by whom. ○ Corrections were not lined out, initialed, explained or, in some cases, substantiated by source. The percentages of coronary artery stenosis on baseline forms were changed for 52% of subjects reviewed, and forms either missed sources to justify the changes and/or contradicted sources in subject files.	organized in one file, for example: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders version 4 (SCIDs), echocardiogram (ECHO), electrocardiogram (ECG), submitted data. If space does not allow for this, notes to files (NTFs) explaining where related sources can be located should be included in subject primary files. Wherever possible or appropriate, headers should be completed, and sticky notes removed and replaced with appropriate NTFs, memos, or initialed and dated corrections on submitted data.	for each subject. The GCP Attributable, Legible, Contemporaneous and Complete, Original and Accurate (ALCOA) standard should be used to help ensure reproducibility.
Specific Protocol Noncompliance	• 92% of subjects reviewed had study visits and procedures missed and/or not performed per protocol. • There were no left ventricular ejection fractions (LVEF) or wall motion score index (WMSI) values during the mental stress test rest periods for most of the audited subjects. These procedures are represented in the protocol as a direct measure of the primary study objective. • Some protocol-mandated office visits were performed by phone. • Mailing drug was not explicitly approved by the IRB, was not explicitly allowed per	• Provide to the IRB a response explaining why LVEF and WMSI were not consistently measured during the rest period after each mental stress test. Describe how this is reflected or qualified in published data. • Submit the abbreviated SCID for IRB approval.	• Create a template or mechanism to log all protocol deviations and mandate its use across all enrolling IITs. PIs should sign off on a monthly basis, implement corrective and preventative action as appropriate, and amend protocols as appropriate. Management should periodically review study deviation logs. • Many unnecessary deviations may have occurred because study practices evolved but the protocol was never updated. Detail the existing process or develop a process for drafting amendments and internally approving them.

	protocol, and there was no shipping documentation on record. • Protocol deviations were not tracked. • Known serious issues, including subject drug lost in the mail and repository blood samples lost for three subjects, were never reported to the IRB. • 35 of 100 SCID subject evaluations were not completed (a required baseline assessment that could affect eligibility). IRB requests to monitor subsequent SCID administration do not appear to have occurred. The abbreviated SCID used for the majority of subjects represents a deviation and was never IRB-approved.		
Consents	• 12.7% of informed consent forms (ICFs) reviewed had at least one issue, including one missing ICF, two ICFs without the Person Obtaining Consent (POC) signature, four ICFs where the POC signatures were illegible and could not be compared to the DOA log, 10 signed but incorrect versions, and one where the informed consent process was not carried out appropriately.	• Report the missing consent for subject 064-000 to the IRB. Generate a NTF indicating the original consent could not be found and the incident was reported to the IRB. • Attempt to obtain signatures from anyone still employed at Duke for the REMIT DOA log. Generate a NTF naming all study personnel for whom signatures cannot be obtained.	• Design a DOA template and mandate use for all pending and currently enrolling Psychiatry IITs. • Establish a system to ensure that study team members have limited/qualified access to previous versions of the consent or are specifically trained to only use the current IRB-approved version. • Implement a standard operating procedure (SOP) that details the roles and expectations for PIs and sub-investigators (sub-Is) during the informed consent process. Consider in-person formal training for faculty and staff on the logistics and importance of the informed consent process.

Continuing Review (CR) Lapse/Subjects Not Re-consented	• REMIT repository trial approval lapsed for eight months. The IRB required the 34 subjects enrolled during the lapse to be re-consented but RCA could not find evidence that this occurred.	• Consult the IRB if it is permissible to use these subject samples or whether existing samples should be destroyed. • If the samples have already been analyzed, work with the IRB to determine if collaborators should be notified of the lapsed approval and failure to notify patients, and advised to destroy samples. • Consult the IRB to determine if subjects should be notified of the lapsed approval and re-consented.	• Not applicable
Safety Review Not Performed	• The IRB mandated a safety review of the first 20 patients before the study opened. RCA did not find evidence that this was performed.	• Provide additional documentation including all IRB correspondence and directives regarding the safety review. Clarify if the request was made as part of the IRB initial review and approval. • If the safety review was completed, provide a copy of documentation. If the review was not performed, generate a NTF indicating the review was not performed.	• Not applicable
Drug Accountability Issues	• There is explicit documentation that 10 of 25 subjects reviewed (40%) were mailed study drug. Another five subjects reviewed (20%) took medication regularly even though they missed visits where medication was dispensed. Mailing drug was not explicitly approved by the IRB, was not explicitly allowed per protocol and no shipping documentation is on record. • One drug calendar used by the subjects reviewed was never approved by the IRB. • One subject's medication was lost in the mail and the subject was sent an additional order. This was not reported to the IRB. There is no documentation indicating how returned drug was stored or destroyed.	• Report lost drug to the IRB. • Provide details on how drug reconciliation and destruction was carried out; include who was responsible for performing pill counts and who was responsible for completing medication count forms. Detail where medication was expected to be stored and describe how unused medication was destroyed.	• All drug diaries instructing subjects how to take medication must be approved by the IRB. For trials that involve oral drugs with specific tapering instructions, consider using a diary designed for subjects to record days/times they took their medication to better track subject compliance. • If the study team, as opposed to the IDS, is responsible for any portion of drug accountability (e.g., counting returned drug and tracking unused medication, recording this on a medication log, destroying returned drug), the trial should have an established written drug accountability

			plan, either in the protocol or a pharmacy manual.
Data and Safety Monitoring Board (DSMB) Documentation	• Protocol mandates that the DSMB evaluate, approve and make recommendations regarding subject safety, progress toward recruitment goals, data quality, treatment plan adherence, participant retention/attrition rates, and any necessary modifications or discontinuation of the study. Minutes were not consistently recorded to document what was reviewed, only very brief approval letters. • The approval letter for the June 2009 meeting was issued February 12, 2010; 55 subjects were consented in that period. • Per protocol, DSMB meetings/approvals must occur annually. Meeting materials prepared for January 2011 were found, but no records that meeting took place were located. Subject enrollment continued through August 2011.	• File in the regulatory binders all additional documentation provided by the external DSMB and all materials and/or minutes generated before or after the REMIT DSMB meetings. • Generate a NTF explaining that permission to continue enrollment was granted verbally at the June 2009 DSMB meeting and the study team continued enrollment based on that.	• Outline the existing internal Psychiatry procedure for determining trials that require DSMBs and how members are appointed and approved. • Include detailed language regarding DSMB membership, expectations and procedures in a DSMB charter, instead of new study protocols. A draft charter should be provided to (and potentially revised by) external DSMB members to clarify their obligations prior to any subject enrollment.
Regulatory Binders	• Electronic and paper binders were incomplete per GCP guidelines. The study team did not have documentation for the initial IRB approval, many study amendment approvals, many approved materials, and study personnel change approvals. • The REMIT Repository trial did not have its own binder and there was no DOA log, nor was there formal confirmation of whom the PI delegated all trial-specific responsibilities to or particular staff responsibilities involved.	• Perform complete reconciliation of the REMIT and REMIT Repository regulatory binders. • Documents housed within the "Regulatory Binder" and "REMIT Audit" files should be consolidated into one electronic regulatory binder that includes electronic copies of everything in the paper binders. The paper binder should be archived except for documents requiring a wet-ink signature. • If missing or incomplete documents in appendix E are found, file in the electronic binder. • Generate NTFs for curricula vitae (CVs), licenses, Collaborative Institutional Training Initiative (CITI) trainings and	• Develop a standard DOA log template and mandate use across all pending and enrolling Psychiatry IITs. • Develop a standard but customizable electronic regulatory binder folder for all pending Psychiatry IITs.

		signatures that cannot be obtained for anyone listed on the DOA or in the eIRB. • Resolve date discrepancies between eIRB and the DOA log. Anyone listed on one document but not the other should now be added.	
Research Data Security Plan (RDSP)	• The RDSP was not created prior to the May 2018 QA review and the existing one is inaccurate. An accurate RDSP ensures that data is stored securely and that auditors can validate actual data storage against a written plan.	• Revise the REMIT RDSP and include information regarding paper source document worksheets used as scanned data forms. • Specify in the RDSP how access to the electronic database is limited and controlled. • Delete information about who needs to be present during testing.	• Consider providing RDSP training for future study teams. • Consider providing training on writing RDSPs to staff who will routinely do so.
Violations of Duke Social Security Number (SSN) Usage Policy	• RCA found multiple policy violations including SSNs on health release forms, 28 Accounts Payable Check Request Forms and Excel spreadsheets of patients contacted about study participation.	• Follow recommendations of the OARC Privacy unit assessment to be performed subsequent to the RCA review.	• If relevant to future studies, ensure teams review the Duke SSN Usage Policy.